

REMARKS

Claims 1-19 were pending. By this Amendment claims 2, 4-6 and 8 have been canceled. Claims 1, 9-13 and 17 have been amended. Accordingly, the claims now pending are claims 1, 3, 7 and 9-19.

Applicants appreciate the acknowledgment by the Office that the subject matter of original claims 2, 3, 7-13 and 18-19 is patentable over the prior art of record. Independent claims 1 and 17 have been amended to recite an attenuated strain of vesicular stomatitis virus (VSV), as in original claim 8, to overcome the art rejections and some of the grounds of the enablement rejection. Other amendments were made to overcome the rejections under Section 112, second paragraph. Applicants' arguments with respect to the remaining grounds for the enablement rejection are set forth below. As discussed below, the specification enables the use of VSV to reduce the viability of melanomas.

The specification has been amended to contain the sequence identifiers. Support for the amendment of the specification can be found, *inter alia*, in Figures 14-23.

Applicants respectfully submit that the amendments are fully supported by the disclosure and do not raise an issue of new matter. Entry of the amendments is respectfully requested.

CONSIDERATION OF INFORMATION DISCLOSURE STATEMENT

The Office Action stated, "The Information Disclosure Statement filed on 4-1-2004 is acknowledged. . . . It should be noted that not all of the cited references were available and consequently were not considered. Said references will be considered as they become available." (January 11, 2005 Office Action, page 2). An Information Disclosure

Statement, including copies of the documents cited therein, is being filed concurrently herewith.

SEQUENCE COMPLIANCE

The Office Action stated that “Figures 14-23 contain sequences without the requisite sequence identifiers.” (January 11, 2005 Office Action, page 2). In response, the Brief Description of Figures 14-23 has been amended to contain the sequence identifiers. MPEP 2422.02 (8th ed., Rev. May 2004), p. 2400-34 (“. . . the sequence identifier . . . must be used, either in the drawing or in the Brief Description of the Drawings.”)

INVENTION IS ENABLED

Claims 1-19 have been rejected under 35 USC §112, first paragraph, as allegedly not being enabled by the specification. This rejection is respectfully traversed.

The Office has taken the position that “the specification, while being enabling for methods utilizing VSV for reducing the viability of cell lines *in vitro*, and the use of VSV to reduce the viability of tumor cell based xenographs in immunodeficient mice, does not reasonably provide enablement . . . for the reduction of viability of all types of melanoma tumor cells (either *in vivo* or *in vitro*) or . . . in an immunocompetent animal.” (January 11, 2005 Office Action, pages 2-3).

First, the Office has improperly sought to place on applicants the burden of proving that the invention works. Although the Office has acknowledged that “the specification provides great detail on the susceptibility of different cell types to VSV and the protective effect of alpha interferon against VSV infection. . . .” (January 11, 2005 Office Action, pages 4-5), the Office considers that insufficient because the amount of experimental proof is allegedly insufficient. The rejection states:

“Additionally, the instant claims are drawn to all forms of melanoma tumor cells, while the specification has demonstrated only a single melanoma cell line (SK-MEL3) that is susceptible to VSV infection. (see Table 1 and page 28 of the specification) and said melanoma cell line was shown to be rapidly destroyed by VSV infection in vitro (see Table 2 [sic, Table 1] and page 28 of the specification).”

(January 11, 2005 Office Action, page 5) (underlining added).

Contrary to the clear implication of the rejection, applicants are not required to submit experimental results demonstrating the anti-tumor activity of vesicular stomatitis virus. Rather, the Office bears the burden of establishing that the specification does not satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. As stated by the CCPA in In re Marzocchi:

“As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.”

In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, ____ (underlining added). It is not sufficient for the Office to simply assert that it doubts the correctness of the statements in the disclosure. The Office must back up its doubts with evidence or reasoning. Again from In re Marzocchi:

“In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.”

In re Marzocchi, 439 F.2d at 224, 169 USPQ at ____ (internal citations omitted) (underlining added). No evidence or reasoning has been cited in support of the rejection. The mere insertion of the word “only” before a recounting of what applicants have shown experimentally does not qualify as acceptable evidence or reasoning to sustain an enablement rejection. To the contrary, the demonstrated success in a variety of melanoma tumor cell lines supports applicants’ position that the invention works for its intended purpose.

All or virtually all melanoma tumor cells can be treated in accordance with the method of this invention. In addition to the specification, ample data from other sources also supports the claim that melanoma cancers are, in general, appropriate targets for therapy with VSV. A number of different melanoma cancer cell lines were tested in many different experiments, both *in vitro* and *in vivo*, and found to be susceptible to VSV (Table A below).

Table 1. Examples of *in vitro* and *in vivo* anti-melanoma activity by VSV.

Melanoma Cell Line(s)	Reference
SK-MEL-3	WO 02/00233, Example 3 on page 19. Instant specification, Examples 16, 18 and 25.
Various	<i>In vitro</i> and <i>in vivo</i> activity noted in Stojdl DF et al., 2003. <i>Cancer Cell</i> 4:263-275.
B16(F10)	<i>In vitro</i> and <i>in vivo</i> activity noted in Fernandez et al., 2002, <i>J Virol</i> 76:895-904

Moreover, the specification teaches the method by which one skilled in the art would screen a particular melanoma cancer to confirm its sensitivity to VSV. The level of routine testing taught in the application is well within the capabilities of one skilled in the

art, and would not require undue experimentation. All of the components required for testing are disclosed and no special or unique manipulations are involved.

Second, the rejection assumes, without foundation, that VSV does not possess antitumor activity against melanoma tumors generally and then faults applicants for not providing guidance as to which carcinoma tumors are susceptible and which are immune to the antitumor effects of VSV. Thus the rejection states:

Moreover, the specification is . . . silent on what other melanoma tumor cell types are killed by VSV infection. The invention seems to be predicated on the susceptible tumor cells lacking PKR activity, but the specification is silent on which melanoma tumor cells lack said function.

(January 11, 2005 Office Action, page 5). This position would be well taken if VSV lacked antitumor activity against melanoma cancers generally. However, since VSV has antitumor activity against all or virtually all melanoma tumor cell types, a list of the melanoma tumor cells that are susceptible to the anti-tumor effects of VSV would be identical or virtually identical with a recitation of melanoma tumor cells. Applicants chose not to unnecessarily burden the specification in this way, for which they deserve praise rather than criticism in accordance with the well-established principle that “a patent need not teach, and preferably omits, what is well known in the art.” (Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, __ (Fed. Cir. 1986), *citing* Lindemann Maschinenfabrik v. American Hoist and Derrick, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984)).

The specification teaches that “VSV has a broad host range and is capable of infecting most types of human cells, whereas other viruses are more limited in regard to the types of cells they may effect”. (Specification, page 6, lines 27-29). In view of the broad host range of VSV, the person of ordinary skill in the art would not require undue experimentation to practice the invention.

Third, the Office has also improperly tried to place on applicants the burden of proving that the invention works *in vivo*. The rejection stated:

“People of skill in the art require evidence that a benefit can be derived by the therapeutic application of a given substance; however a survey of the relevant art does not indicate that substances such as those claimed provide such benefit. The instant specification fails to provide significant direction on which viruses, if any, are capable of eliciting a therapeutic response (tumor cell death) when administered to an immunocompetent subject in need.”

(January 11, 2005 Office Action, pages 5-6). Based on the above-quoted passage from the rejection, one might think that the application contains no *in vivo* results, but it does. The specification contains *in vivo* data demonstrating the efficacy of VSV in treating human melanoma xenografts in nude mice. (Examples 16, 18 and 25, on pages 42-44 and 49).

The Office argues that “Example 25 is insufficient to provide enablement for the full breadth of the instant claims.” (January 11, 2005 Office Action, page 8). It is contrary to the law to require that enablement be provided by a single example, taken in isolation. Rather it is the specification as a whole that must enable the claimed invention. (35 U.S.C. §112, first paragraph). Thus, it is improper to take the examples one-by-one as the rejection has done, purport to find each one insufficient to enable the full breadth of the claimed invention, set it aside, and then repeat the process with the remaining examples. Moreover, the faults the rejection purports to find with Example 25 are not well taken.

The rejection stated that the demonstrated efficacy of “two mutated VSV viruses [against] cell-line based xenographs in immunodeficient mice. . . cannot be extrapolated to the use of wild-type (non-mutated) VSV against established tumors in an immunocompetent animal.” (January 11, 2005 Office Action, page 8). Cell lines implanted into athymic mice are not only an acceptable model but a standard by industry

and the National Cancer Institute (NCI) for determining antitumor efficacy of a novel anticancer agent. Three anticancer agents recently approved by the U.S. FDA had earlier showed activity against xenografts of human tumor cell lines (Table B). While no model is perfect, Winograd concluded that there is “a good predictability of a panel of human tumor lines for clinically effective drugs” and that “the application of human tumor xenografts in anticancer drug development is warranted.” (B. Winograd, et al., “Human tumor xenografts in the nude mouse and their value as test models in anticancer drug development (review)” *In Vivo* (1987) 1: 1-14, Abstract on p. 1). In the oncology reference Cancer Principles & Practice of Oncology (2001; 6th edition; editors: DeVita VT, Jr; Hellman S, and Rosenberg SA)), Chu et al (Section 19.2, para. bridging pp. 352-353) indicate that as part of the standard NCI development scheme for new cancer drugs, the human tumor cell line most sensitive to an active candidate *in vitro* is selected for testing *in vivo* as a xenograft in a subcutaneous implant site in a nude mouse. The U.S. FDA accepts positive tumor xenograft results as a sufficient level of preclinical activity when approving a clinical trial for an investigational new drug (IND).

Table B. The Sensitivity of Human Tumor Xenografts in Athymic, Nude Mice to Recently FDA-Approved Cancer Agents

Recently Approved Cancer Drug	Indication	Effects in Athymic Nude Mouse Tumor Model	References
Gefitinib (Iressa, a small molecule inhibitor of EGFR)	Lung cancer	Potent activity against human lung cancer xenograft model	Raben D, et al., Semin Oncol. 2002 Feb;29(1 Suppl 4):37-46.
Bortezomib (PS-341, a proteasome inhibitor)	Myeloma	Significant <i>in vivo</i> antimyeloma activity in human tumor xenograft model	LeBlanc R, Cancer Res. 2002 Sep 1;62(17):4996-5000
Cetuximab (Erbitux, a monoclonal antibody against EGFR) in combination with irinotecan	Colorectal cancer	Regressions of human colorectal cancer xenografts noted with the combination of cetuximab and irinotecan	Prewett MC et al., 2002, Clin Cancer Res 8:994-1003

The rejection stated that “said example only utilizes two of the five VSV mutants disclosed in the instant specification suggesting that the anti-tumor effect of the disclosed VSV mutants is unpredictable.” (January 11, 2005 Office Action, page 8). While Example 25 uses 2 mutant strains of VSV, the five mutants disclosed in the specification were tested in Example 20 and all five were found to have *in vitro* antineoplastic activity. Example 20 demonstrates that all five strains are selective at *in vitro* killing of tumor

cells compared to normal cells. The testing of two VSV mutants in Example 25 and finding potent systemic activity with both of them only adds to the predictability of the anti-tumor effects of VSV and does not undermine it. It would be unreasonable to conclude that the other three mutant strains would not work *in vivo*.

Moreover, the rejection has tried to shift the enablement burden to applicants by putting the Office's unsupported doubts in the mouth of "people of skill in the art" who are said to "require evidence that a benefit can be derived by the therapeutic application [i.e. *in vivo*] of a given substance." (January 11, 2005 Office Action, p. 5). This citation to "people of skill in the art" obscures such crucial issues as which people require such evidence, whether they are a minority or a majority of those of skill in the art, what evidence would they consider adequate, and the purpose for which they require such evidence. The purpose for which they allegedly require the evidence is necessary to avoid improperly importing into the enablement context the more stringent requirements under the Food and Drug Act for approval to market a therapeutic agent. It is, of course, important not to confuse "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." In re Brana, 51 F.3d 1560, 1567, 34 USPQ2d 1436, _____ (Fed. Cir. 1995), citing, Scott v. Finney, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994).

By attempting to require applicants to demonstrate that the invention "provide[s] . . . benefit" (January 11, 2005 Office Action, page 5), the Office is trying to impose a kind of super-utility standard, contrary to the law which places on the Office the burden to show otherwise. In re Marzocchi, 439 F.2d 220, 223-224, 169 USPQ 367. Even if the Office is applying a less rigorous standard than the "safe and effective" standard under the Food and Drug Act, it is nevertheless exceeding the mandate conferred on the PTO by the patent laws.

The Office has attempted to require applicants to prove that the *in vitro* data contained in the specification correlate to an *in vivo* benefit. The rejection stated:

“[T]he specification . . . does not provide any basis for correlating the *in vitro* results with beneficial effects that could reasonably be expected when said viruses are administered *in vivo* to ‘treat’ melanoma tumor cells, although *in vivo* use is clearly encompassed by the claims. Lacking either direct evidence for *in vivo* benefit, or a reasonable basis for correlating the *in vitro* data as exemplified in the instant specification with *in vivo* benefit . . . the specification cannot be said to teach how to use the claimed viruses as pharmaceuticals without undue experimentation.”

January 11, 2005 Office Action, paragraph bridging pages 6-7. Applicants respectfully submit that it is accepted in the art to which this invention pertains that *in vitro* evidence of antitumor effect on tumor cell lines is reasonably correlated to *in vivo* therapeutic efficacy. This is shown by the Winograd paper discussed above, and the accepted utility of the NCI Tumor Cell Panel also discussed above, which demonstrates that cell culture-based assays provide are correlated with clinical utility. The correlation is further illustrated by Pecora, et al., *J. Clin. Oncol.* (2002) 20(9): 2251-2266. It is also illustrated by U.S. Patent No. 5,677,178 (McCormick). The only experimental results contained in McCormick are the results of *in vitro* testing (Patent No. 5,677,178, column 18, line 42 to column 20, line 23; and Figures 2A-3C). Nevertheless McCormick bases his teaching of human therapy on those *in vitro* results (Patent No. 5,677,178, column 16, line 45 to column 18, line 25). McCormick, like so many others, considered *in vitro* results to support his teaching of human therapy.

The Office has cited several articles, which together demonstrate nothing more than the unsurprising observation that the *in vitro* environment cannot duplicate the *in vivo* environment exactly. Nevertheless, it is undeniable that *in vitro* experiments continue to be performed and relied upon to identify treatments for *in vivo* use. If the rejection was correct that “clinical correlations are generally lacking” (January 11, 2005 Office Action, page 7), *in vitro* experiments would not be as widely used as they are.

Moreover as mentioned above, the specification does contain *in vivo* data demonstrating the efficacy of VSV in treating human melanoma xenografts in nude mice. (Examples 16, 18 and 25). These results support applicants' position that the *in vitro* activity of VSV is correlated with *in vivo* efficacy.

The *in vivo* anticarcinoma activity of VSV has been demonstrated. See Specification, Examples 16, 18 and 25; and Table A above. This demonstrated success confirms the correlation between the *in vitro* and *in vivo* anticarcinoma activity of VSV.

Fourth, the Office improperly sought to place on applicants a separate burden of explaining the mechanism by which the claimed invention works. This rejection stated, "The specification is silent on what receptor is utilized by VSV . . . for cell entry. . . ." (January 11, 2005 Office Action, page 5). As seen from the above-quoted passage, the Office has taken the position that the specification is required to explain how the viruses of the claimed invention enter the cells that they infect. That position is contrary to law because, "it is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests, nor is the inventor's theory or belief as to how his invention works a necessary element in the specification to satisfy the enablement requirement of 35 U.S.C. §112." Cross v. Iizuka, 753 F.2d 1040, 1042, 224 USPQ 739, ____ (Fed. Cir. 1985), citing Fromson v. Advance Offset Plate, Inc., 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983).

Fifth, the Office has improperly sought to build an enablement rejection out of qualified statements in the specification concerning mechanism. The rejection stated, "The invention seems to be predicated on the susceptible tumor cells lacking PKR activity, but the specification is silent on which melanoma tumor cells lack said function." (January 11, 2005 Office Action, page 5). Contrary to the above-quoted assertion from the rejection, applicants' invention is not limited to tumor cells that lack PKR activity. No such limitation appears in claim 1. The statement in the specification that "[p]referably

the tumour cell lacks PKR activity" (Specification, page 4, lines 8-9) (underlining added) is further evidence that the invention as a whole is not "predicated on the susceptible tumor cells lacking PKR activity". Understanding the instant invention as being "predicated on the susceptible tumor cells lacking PKR activity" is all the more unreasonable in view of applicants' express warning that their discussion of PKR's possible role was being advanced "[w]ithout being bound by theory" (Specification, page 14, lines 14-18, esp. line 14).

Sixth, the Office has faulted the specification for allegedly being silent with regard to routes of administration. The rejection stated:

[T]he specification is . . . silent on how said viruses are to be administered to said subject."

(January 11, 2005 Office Action, page 6). All conventional techniques and routes of *in vivo* administration can be utilized. Other than claim 16, the invention as claimed does not rest on the selection of certain routes of administration from among those known in the art.

The allegation that "the specification is . . . silent on how said virus is to be administered . . ." (January 11, 2005 Office Action, page 6) is wrong. The specification does indeed provide numerous examples of the successful administration of VSV by a variety of routes: intravenous injection (Example 25), by intratumoral injection (Examples 5, 16 and 18) and by injection of virus-producing cells into the tumor (Examples 5 and 16).

Both the specification and the published literature since then from the inventors and verified by other academic researchers (see Table C below) have solidified the concept that efficacy is achievable for VSV using many different routes of administration to treat a diverse set of tumors at a variety of locations.

Table C. Various routes of VSV administration are efficacious against malignancies in mice

Route	Citation
Intravenous injection	<u>Specification</u> : Example 25 (and Figure 13)
Intravenous injection	Stojdl DF et al., 2003. Cancer Cell 4:263-275.
Intravenous injection	Balachandran S et al., 2001 J Virol 75:3474-79
Intratumoral injection	<u>Specification</u> : Examples 5, 16, and 18; and Figures 5, 7, and 9.
Intratumoral injection	Balachandran S et al., 2001 J Virol 75:3474-79
Intratumoral injection	Huang T-G et al., 2003 Mol Ther 8:434-40.
Intratumoral injection	Ebert et al., Cancer Res 63:3605-11
Intratumoral treatment with cells infected with VSV	Specification: Examples 5 and 16.

In support of its contention that conventional methodologies to administer VSV would not be suitable for achieving anti-cancer effect, the rejection ignores the anti-cancer evidence in the specification and instead attempts to enlist evidence from the specification relating to toxicity. The rejection states:

The specification illustrates this point on page 33 where it states that PKR-/- mice were killed with VSV by several routes of infection but that these mice were not affected by intravenous injections of the virus.

(January 11, 2005 Office Action, page 6). The contention that the differing toxicities observed in PKR-/- mice following administration of VSV by various routes of administration equates with a similar dependence on route for the intended anti-cancer activity is invalid. Toxicity and efficacy are very different and independent endpoints. The lack of intravenous toxicity does not in any way imply that there would be a lack of

efficacy by this route. Indeed, the specification demonstrates efficacy by the intravenous route (Experiment 25).

Next, the rejection cites Jain, *Scientific American* (July 1994) for the proposition that there are various impediments to delivery of drugs into solid tumors (January 11, 2005 Office action, page 6). While the issues cited in the Jain article may be theoretically interesting, it is important to bear in mind that many anti-cancer drugs have been demonstrated to be effective against solid tumors even when administered intravenously. Moreover, the Jain reference suggests that solid tumors could present a greater hurdle for delivery than leukemia, but any potential impediment for the delivery of VSV to solid tumors has already been overcome using intravenous VSV treatment of solid subcutaneous tumors as illustrated in example 25. Additional results cited in Table C (above) further confirm that VSV has antitumor efficacy when given intravenously to solid tumors in mice.

Moreover, the specification does contain *in vivo* data demonstrating the efficacy of intravenous VSV in treating human melanoma xenografts in nude mice. (Example 25, page 49). Thus in contrast to the rejection's reliance on theoretical concerns that may or may not be valid in any particular case, the specification contains actual experimental results demonstrating the anti-tumor efficacy of VSV administered intravenously.

In view of the foregoing, applicants respectfully submit that the enablement rejection is improper and should be withdrawn.

AVAILABILITY OF VSV MUTANT STRAINS

Claims 9-13 have been rejected under 35 U.S.C. §112, first paragraph, on the grounds that biological deposit is allegedly necessary for the enablement of such claims. This rejection is respectfully traversed.

The rejection states that it “is apparent that the VSV strains M1, M2, M3, M4 and M5 are required in order to practice the invention.” (January 11, 2005 Office Action, page 9). A review of the scientific literature indicates that a variety of researchers have had access to VSV mutant strains. Because the strains are generally available to researchers in the field, applicants respectfully submit that deposit under the terms of the Budapest Treaty is not necessary.

As evidence of the widespread use of these strains, applicants hereby submit copies of the following documents:

- Desforges, et al., Virus Res. (2001) 76(1):87-102 (Abstract).
- Pasternak, et al., Virology (1988) 166(2): 379-386 (Abstract).
- Marcus, J. Gen. Virol. (1980) 47(1): 89-96 (Abstract).
- Ahmed, J. Virol. (2003) 77(8): 4646-4657.
- Winship, J., et al. Gen. Virol. (1984) 65: 843-847 (Abstract).
- Stanners, et al., Cell (1977) 11(2): 273-281 (Abstract).
- Ferran, et al., J. Virol. (1977) 71(1): 371-377.

Desforges reports the use of mutant strains T1026 (M1), TP3 (M3) and G31 (M5). Pasternak and Marcus report the use of mutant strain T1026 R1 (M2). Ahmed reports the use of mutant strains T1026R1 (M2), TP2 and TP3 (M3). Winship reports use of mutant strain T1026R1 (M2). Stanners reports use of mutant strain T1026 (M1). See Specification, page 10, lines 14-16 for a key to the varying nomenclature.

CLAIMS NOT INDEFINITE

Claims 1-19 have been rejected under 35 USC §112, second paragraph, as allegedly being indefinite. There are two grounds for the rejection, each of which has been overcome by amendment as explained below.

Claim 1 was rejected because of the phrase “not a common human pathogen.” The amendment of claim 1 to recite an attenuated strain of VSV, left the objected-to phrase unnecessary. It has, accordingly, been deleted.

Claim 3 [sic, 2] was rejected because of the term “substantially”. The cancellation of claim 2 renders this ground of rejection moot.

The reasons given in the Office Action for the indefiniteness rejection do not apply to claims 17-19. Accordingly, the rejection of claims 17-19 on grounds of alleged indefiniteness is respectfully traversed as being without basis.

DOUBLE PATENTING

Claims 1 and 4-6 have been provisionally rejected for alleged obviousness-type double patenting over claims 1-2 and 6-9 of copending Application No. 10/717,101. Applicants will consider filing a terminal disclaimer when otherwise allowable subject matter is indicated.

CLAIMS ARE PATENTABLE OVER PRIOR ART

Claims 1, 4-6, 14-15 and 17 have been rejected under 35 USC §102(a) as allegedly being anticipated by Roberts et al. (WO 99/18799). Claim 16 has been rejected under 35 USC §103(a) as allegedly being obvious over Roberts et al. (WO 99/18799) in view of Molnar-Kimber (WO 99/45783). These rejections are respectfully traversed.

Claims 1 and 17 have been amended to recite “an attenuated strain of vesicular stomatitis virus” as in original claim 8, which the Office has found to be patentable over the prior art. None of the cited references disclose or suggest an attenuated VSV. Accordingly, applicants maintain that the art rejections have been overcome.

CONCLUSION

Reconsideration and withdrawal of all rejections and objections is respectfully requested. It is believed that no fee, other than the extension of time fee, is required in connection with the filing of this Amendment. If any additional fee is required, the Commissioner is hereby authorized to charge the amount of such fee to Deposit Account No. 50-1677.

Respectfully submitted,


Lewis J. Kreisler
Reg. No. 38522
Attorney for Applicant(s)

930 Clopper Road
Gaithersburg, MD 20878
Phone: (240) 631-2500 x3276
Facsimile: (240) 683-3794

Enclosures: WO02/00233
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